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Research Article

Concurrent radiotherapy and weekly gemcitabine treatment of locally advanced squamous cell carcinoma of head and neck

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ABSTRACT

Head and neck cancers are not curable yet but survival and local control has been increased due to concurrent treatment approach. Study was conducted to assess the role of concurrent Gemcitabine (2'2' Difluro Deoxycytidine) along with radiotherapy in treatment of Head and Neck cancers and to assess local control as well as disease free survival achieved due to chemoradiation. 100 patients were enrolled in this study, 50 patients received Radiotherapy (Group A- Control group) alone and 50 patients received Concurrent Chemoradiotherapy (Group B- Study group). Patients in study group received Gemcitabine 200mg/m^2 on weekly basis for 5-7 cycles over 30 mins. Radiation delivered after 2 hours of IV infusion. Conventional radiotherapy was given in dose ranging from 66-70Gy in 33-37# for 6-7weeks. In this study, Grade 3 mucositis and Grade 2 pharyngeal toxicity were common i.e, 56% and 54% respectively in study group and 30% and 38% respectively in control group. Hematological toxicity i.e., Grade 1 leucopenia was seen in 28%. Even though the toxicities were high in study group compare to control group but they were tolerable and acceptable. The response was better in concurrent group than radiotherapy alone (Control group) CR 52% vs 40%, PR 34% vs 36% and SD 14% vs 24%. Concurrent use of gemcitabine and radiotherapy is a effective modality in treatment of head and neck cancers with acceptable toxicity. Improved local control shows that Gemcitabine acts as a sensitizers and has synergistic action along with radiotherapy.

Keywords: Gemcitabine, Radiotherapy, Locally advanced Squamous cell carcinoma of Head & Neck

INTRODUCTION

Head and neck cancers constitute 5% of all cancers worldwide. In our department 26% of head and neck cancers were observed in 2007 statistics and 28% in 2008. These cancers are a major cause of morbidity and mortality in the Indian population, which accounts are above 50 % of all malignant tumours. Most of the patients present with locally or locoregionally advanced disease. As a result of their location, these tumours can cause varying degree of functional and cosmetic deformity that are often exacerbated by cancer treatment. From 1960 to 1980 surgery and radiation therapy, after post operative, remained the primary modalities used to treat these tumours. Larynx preservation trial 1991[1], the non surgical organ preservation through the radiation and chemotherapy entered the main stream. Since then the most significant advances in the treatment of head and neck tumours have been the development of altered radiation fractionation schedules and concurrent chemotherapy regimes that have documented improvements in local control and overall survival.

The administration of chemotherapy during radiotherapy is commonly referred to as concurrent chemoradiation or simply chemoradiation. This approach is now the standard care in most of the locally advanced cancers of head and neck. Based on result of multiple randomized trials that have documented survival benefit, Chemoradiation appears to confer a survival benefit over

radiotherapy alone in the both "unresectable" setting as well as the postoperative setting.

In general, most trials of concurrent chemoradiation have not documented reductions in the rates of distance metastases with the addition of concurrent chemotherapy to radiotherapy. As a result, the survival benefit imparted by chemotherapy is primarily due to improvements in local control.

Combined chemotherapy and radiotherapy have become the standard treatment for locally advanced unresectable squamous cell carcinoma of head and neck.[2] Five different randomized trials in unresectable patients have given positive results and have shown improved survival and improved loco-regional control. A recent meta-analysis has also shown absolute survival advantage in patients treated with concurrent chemo-radiotherapy. However a controlled mucosal and haematological toxicity is noted in these patients.[3]

A number of old trials have used radiotherapy concurrent with single radiosensitizing cytotoxic agent like 5FU, methotrexate, and cisplatin. Among them Gemcitabine, a pyrimidine analogue is one such chemotherapeutic agent which has shown radiosensitization at non cytotoxic concentration of 10nmol/l. It has been shown that premedication exposure of HT-29 human colon carcinoma cells to non toxic concentrations of gemcitabine for 24 hrs achieves a sensitizer enhancement ratio of 1:8.[4] Pancreatic and breast cancer cell lines have also shown significant radiosensitization.[5,6]

Based on these preclinical studies it has been postulated that radiosensitization with Gemcitabine is due to depletion of deoxyadenosinetriphosphate (dATP) through inhibition of radionucleotide reductase by the diphosphate metabolite, dFdCDP, and cell cycle distribution into S phase. When these two conditions are present, DNA damage caused by radiation cannot be repaired and leads to cell death.

Phase III clinical studies in squamous cell carcinomas of head and neck have also been done. They used doses ranging from 50-300mg/m2 during radiotherapy and achieved high overall toxicity. These studies have emphasized the need for further evaluation of radiosensitization by low dose Gemcitabine.[7] So trial conducted to find out feasibility and toxicity of concurrent administration of 150 mg/m2 of Gemcitabine and radical Radiotherapy in patient with locally advanced squamous cell carcinoma. Different studies have shown concurrent use of radiotherapy and Gemcitabine is effective in treating locally advanced head and neck cancers.[8,9]

Aims

1. To assess the role of concurrent Gemcitabine along with radiotherapy in treatment of Head and Neck cancers
2. To assess local control as well as disease free survival achieved due to chemoradiation.
3. To assess toxicity due to chemotherapy (Gemcitabine) as well as radiotherapy.

Objectives

1. To establish concurrent Chemoradiation as an effective modality treatment in Head and Neck cancers.
2. To establish Gemcitabine as a radiosensitizer as well as synergistic agent along with Radiotherapy.

METHODS

This prospective comparative study was conducted in the out-patient department of Radiotherapy and Oncology, Pravara Rural Hospital, Loni. Patients were randomly selected during the period July 2008 to July 2009.

Patients were divided into two groups as, Group A (Radiotherapy alone) and Group B (concurrent radiotherapy and chemotherapy with Gemcitabine).

Eligibility Criteria

1. Histopathologically proven Squamous Cell Carcinoma of head & neck.
2. Karnofsky Performance status >60%
3. Age <60years
4. No history of prior treatment like surgery, chemotherapy, radiotherapy for present disease.
5. Locally advanced cases (stage III onwards)
6. Normal Haemogram, Renal and Liver function.
7. Normal chest X-ray.
8. Written informed consent.

Table 1: Patient characteristics.

Age	**Median**	**50 yrs**
	Range	**30-70 yrs.**
Sex	Male	42 (84%)
	Female	8 (16%)
KPS	>80	12 (24%)
	70-80	38 (76%)
Addiction	Tobacco	45 (90%)
	Non Tobacco	5 (10%)
Tumour site	Oral Cavity	33 (66%)
	Oropharynx	11 (22%)
	Hypopharynx	5 (10%)
	Maxilla	1 (2%)
Stage	III	47(94%)
	IV	3 (6%)

Primary disease status was assessed by Inspection, indirect laryngoscopy, if necessary USG Neck, CT scan.

Lymph node status assessed by TNM staging. Before each cycle of chemotherapy complete blood examination was done – Haemoglobin, Total and Differential count, Platelets, Renal and liver function.

Treatment Schedule

Patient in study group received Gemcitabine 200mg/m^2 on weekly basis for 5-7 cycles. It was diluted in normal saline to make a solution of 10mg/ml and administered intra venous over 30mins. Radiation delivered after 2hours of infusion.

Conventional radiotherapy was given dose ranging from 66-70Gy in 33-37# for 6-7weeks. Two lateral opposed portals or 2 lateral & 1 anterior field with Co^{60} beam was used for primary tumour. Spinal cord excluded after 45Gy with field reduction.

The control group received only radiotherapy, supportive treatment given whenever necessary.

Evaluation & follow up

Every week during treatment, patient were evaluated for general condition, skin reactions, mucosal toxicities. According to RTOG criteria Radiation toxicity were noted and drug toxicity noted as per WHO norms. After completion of treatment patients were examined and then examined every 15 days first until 3 months and then monthly for next 3 months. Accordingly investigations done if necessary. Two patients developed grade IV toxicities for which rest for one week was given

Response

Response was recorded as Complete Response (CR), Partial Response (PR), Progressive disease (PD) or Stable Disease (SD). If there was complete disappearance of all visible and palpable tumour without evidence of distant metastasis after completion of therapy then it was considered Complete Response (CR). If there is >50% regression of tumour then they were considered as Partial Response (PR). And rest were considered as Stable Disease (SD) or Progressive Disease (PD) if there was progression of tumour or appearance of distant metastasis.

Statistical analysis

All recorded data was entered MS Excel and analysed in the form of percentage and proportions whenever appropriate.

RESULTS

Out of 100 patients, 50 received Radiotherapy (Group A) alone and 50 received Concurrent Chemoradiotherapy (Group B). After 6 months of completion, response compared between two groups.

Table 2: Response.

	CR	PR	SD
Group A	20 (40%)	18 (36%)	12 (24%)
Group B	26 (52%)	17 (34%)	7 (14%)

Value of chi-square test = 2.13, p>0.05, not significant

Table 3: Acute radiation toxicity, RTOG criteria.

Toxicity	*Grade1 – No.(%)*		*Grade2 – No.(%)*		*Grade3 – No.(%)*		*Grade4 – No.(%)*	
	A	***B***	***A***	***B***	***A***	***B***	***A***	***B***
Mucosal	11 (22%)	5 (10%)	24 (48%)	6 (20%)	15 (30%)	28 (56%)	--	3 (6%)
Pharyngeal	15 (50)	5 (16.6%)	14 (46.6%)	12 (40%)	1 (3.33%)	3 (10%)	--	--
Skin	6 (12%)	24 (48%)	3 (6%)	7 (14%)	--	--	--	--

Value of chi-square test = 22.34, p <0.05, significant

Table 4: Acute drug toxicity (WHO Norms).

Toxicity	*Grade1 – No.(%)*	*Grade2 – No.(%)*	*Grade3 – No.(%)*	*Grade4 – No.(%)*
Leucopenia	14 (28%)	11 (22%)	--	--
Nausea/ Vomiting	24 (48%)	6 (12%)	3 (6%)	--
Fever	20 (40%)	11 (22%)	--	--

Value of chi-square test = 8.94, p<0.05, significant

DISCUSSION

In developing countries like India more than 50% of Head & Neck Cancer present with advanced disease and usually carry a poor prognosis. This gives a challenge to the Radiation Oncologist in treating such type of patients. Radiation alone may not be sufficient to treat the primary as there are areas of hypoxia which may lead to decreased radiosensitisation.

A 90% of overall response rate was achieved in this study for patients with advanced Head and Neck Squamous Cell Carcinoma. This response is comparable to those achieved with concomitant 5FU, Cisplatin and Radiotherapy but with increased toxicity.

In a phase II study, utilising 200mg/m2 of Gemcitabine during radiotherapy, a 70% overall response rate with 15% complete response was seen.

Shaharyar[10] et al conducted study with 39 patients with overall response rate of 94.3%, partial response of 71.4%, and complete response of 22.9%. Grade 3 mucositis was seen in 71.8%, Grade 4 in 2 patients. Pharyngeal toxicity was the second most common toxicity, Grade 3 in 15.4%.

Ashok Chauhan[11] et al treated 80 patients which were divided into two groups, 40 received only Radiotherapy and 40 received concurrent chemoradiotherapy. The rates of CR and PR were 42.5% and 57.5% respectively for only radiotherapy group and 62.5% and 37.5% respectively for chemoradiotherapy group. There was no significant difference in the response rates at the end of treatment but disease free survival was better in the concurrent group (63.3% vs 20%). 9 out of 17 patients with CR in the radiation group developed relapse while no relapses were seen in concurrent group.

P M Spencier et al evaluated 22 patients out of 29 included in study, CR and PR was 50-50%. Haematological toxicity was mild, but non haematological toxicity was severe: Grade 3-4 stomatitis occurred in 85%, dermatitis in 69%, pharyngitis / esophagitis in 81% and 80% of patients needed a feeding tube during treatment.

J Aguilar Ponce[12] et al, treated 27 patients with locally advanced Head and Neck Cancer, severe mucositis Grade 3-4 in 74% patient and Grade 4 in 41%. Severe haematological toxicity was uncommon. Mild to moderate Xerostomia was most common, late toxicity was seen in 23 patients (85%). The rate of CR is 61%, PR is 27% and ORR 88%. Median follow up of 13 months, 3 year Progression Free Survival and Overall Survival were 37% and 33% respectively. The only variable associated with prolonged survival was the degree of response.

Nagraj G. Huilgol et al.[13] included 15 patients with histologically proven SCC of Head and Neck, Oesophagus and Cervix. Patients were chemonaive. In their study all patients of Head and Neck expressed grade III or IV mucositis at various points of time. All patients finished radiation to the intended dose. Six of seven patients of head and neck cancer that is 85% had complete response.

JD Raguse, HJ Gath et al[14] conducted study on 10 heavily pretreated patients with recurrent & incurable SCC of Head and Neck who were treated with Gemcitabine. In their small phase II study, Gemcitabine demonstrated a high antitumoral activity in SCC of Head and Neck, with a favourable toxicity profile. One Complete Remission, 2 Partial Remission, 3 Stable Disease, were observed yielding a Response rate of 37.5 %. Median survival was 8 months. The incidence of hematological toxicity was low with grade III & IV neutropenia less than 10%.

In our study, Grade 3 mucositis and Grade 2 pharyngeal toxicity was common i.e., 56% and 54% respectively in study group and 30% and 38% respectively in control group. Haematological toxicity, Grade1 leucopenia was seen in 28%. Despite vigorous symptomatic and supportive care, acute toxicities led to interruption of treatment in 8% patients and later treatment was started after one week gap.

Even though the toxicities were high in study group compared to control group but they were tolerable and acceptable. The response was better in concurrent group than radiotherapy alone group CR 52% vs 40%%, PR 34% vs 36% and SD 14% vs 24%.

CONCLUSION

Concurrent use of gemcitabine and radiotherapy is an effective modality in treatment of head and neck cancers with acceptable toxicity. Improved local control shows that Gemcitabine acts as a radiosensitizer and has synergistic action along with radiotherapy.

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REFERENCES

1. Induction CT + RT compound with surgery + radiation in patient with advanced laryngeal cancer. The Department of veteran affairs laryngeal cancer group. N Engl. J. Med. 1991; 324(24):1685-1690.
2. Schantz SP, Harrison LB, Forastiere AA, Tumours of nasal cavity and paranasal sinuses, nasopharynx, oral cavity and oropharynx. In: Devita VT, Hellman

S, Rosenberg SA, editors. Cancer: principles and practice of Oncology, sixth edition, Philadelphia, Lioppincott Willam and Wilkins 2001; 804-14.
3. Pignon JP, Bourhis J, Demenge C, et. al. Chemotherapy as an adjunct to definitive locoregional treatment for head and neck squamous cell carcinoma : Results of three meta- analysis using updated individual data. Lancet 2000; 355:949.
4. Shewach DS, Hahm TM, Chang E. Metabolism of 2-2-Difluro-2-Deoxycytidine and radiation sensitization of human colon carcinoma cells. Cancers Research 1994; 54:3218-23.
5. Lawrence TS, Chang EY, Hahn TM. Radio-Sensitization of pancreatic cell by 2-2-Difluro-2-Deoxycytidine. In J Radiat Oncol Biol Phys 1996; 34: 867-72.
6. Zang XL, Yang SL, Ashamalla H, Rafla S. Gemcitabine induced radiosensitization of human breast cancer cells. Proc Am Clin Oncol 1998; 17A1732.
7. Wildfang I, Roub M, Gunner SA, Issing PH et al: Low dose Gemcitabine with Radiotherapy in advanced head and neck and thyroid tumours. A Phase 11 study. Proc Am Soc Clin Oncol 1999;1550:401a
8. Avraham Eisbruch, Donna S. Shewach, Carol R. Bradford, James F. Letlles, Theodore N. Teknos, Douglars B. Chepeha et. al. Radiation concurrent with Gemcitabine for locally advanced head and neck cancers. A phase I trial and intracellular drug incorporation study. J Clin Oncol Feb 2001; 19(3):792-799.
9. Posner MR; Paradigm shift in the treatment of head and neck cancer: the role of neoadjuvant chemotherapy. Oncologist 2005;10(suppl.3):11-19.
10. Shaharejar, Abrar Ahmed Jawed et al. A Phase II study of Gemcitabine concurrent with radiation in locally advanced Squamous cell carcinoma of Head & Neck: Article of the cancer research group Pakistan. Pak J Med Sci. July-Sep. 2006;22:258-264.
11. Ashok Chauhan et al. Gemcitabine concurrent with radiation therapy for locally advanced head and neck carcinoma. African health Sciences,2008; 8(3):149-155.
12. Aguilar – Ponce, J'; Granados – Garcia, M2; Villaviconcio, V2; Poctevin – Chacon, A3; Green, D4 Duenas – Gonzalez, A5; et al. Phase II trial of Gemcitabine concurrent with radiation for locally advanced squamous cell carcinoma of head and neck. Annals of oncology, Feb.2004; Vol15(2), pp. 301-306(6).
13. Nagraj G. Huilgol, et al. Gemcitabine once a week with radiacal radiation – A Phase 1 Trial: JCRO Vol.2, No2, 30-33 June 2002.
14. JD Raguse, HJ Gath et.al., Gemcitabine in the treatment of Advanced Head & Neck Cancer., Clinical Oncology, Vol.17, Issue 6, P 425-429., Sept. 2005.
15. Lawrence TS, Eisbruch A, Shewach DS. Gemcitabine mediated radiosensitization. Semi Oncol 1997;24(suppl 7):S7-24-S7-28.
16. Lawrence TS. Radiosensitizing nucleosides. Am Soc Clin Oncol 1999;156.
17. Forastiere AA, Trotti A. Radiotherapy and concurrent chemotherapy : A strategy that improves locoregional control and survival and in oropharyngeal cancer. J Natl Cancer Inst 1999;91(24):2065-2066.
18. Pfister DG, Ang K, Brockstein B, et al. NCCN Practice guidelines for head and neck cancers. Oncology (Willitston park) 2000;14(11A):163-194.
19. Bourhis J, Amand C, Pignon JP, Group M-NC. Update of MACH-NC (metaanalysis of chemotherapy in head and neck cancer) database focused on concomitant chemotherapy. J Clin Oncol 2004;22:489s.
20. Forastiere AA, Maor M, Weber RS, et al. Long-term result of intergroup RTOG 91-11: A phase III trial to preserve the larynx-induction cisplatin/5-FU and radiation therapy versus concurrent cisplatin and radiation therapy versus radiation therapy. 2006 ASCO Annual meeting proceeding part I. J Clin Oncol 2006;24(18s):abstr.

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